Transcutaneous electrical nerve stimulation: an effective treatment for refractory non-neurogenic overactive bladder syndrome?

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Abstract: PURPOSE: To assess the effect of transcutaneous electrical nerve stimulation (TENS) for treating refractory overactive bladder syndrome (OAB). PATIENTS AND METHODS: A consecutive series of 42 patients treated with TENS for refractory OAB was prospectively investigated at an academic tertiary referral centre. Effects were evaluated using bladder diary for at least 48 h and satisfaction assessment at baseline, after 12 weeks of TENS treatment, and at the last known follow-up. Adverse events related to TENS were also assessed. RESULTS: Mean age of the 42 patients (25 women, 17 men) was 48 years (range, 18-76). TENS was successful following 12 weeks of treatment in 21 (50 %) patients, and the positive effect was sustained during a mean follow-up of 21 months (range, 6-83 months) in 18 patients. Following 12 weeks of TENS treatment, mean number of voids per 24 h decreased significantly from 15 to 11 ($p < 0.001$) and mean voided volume increased significantly from 160 to 230 mL ($p < 0.001$). In addition, TENS completely restored continence in 7 (39 %) of the 18 incontinent patients. Before TENS, all 42 patients were dissatisfied or very dissatisfied; following 12 weeks of TENS treatment, 21 (50 %) patients felt satisfied or very satisfied ($p < 0.001$). No adverse events related to TENS were noted. CONCLUSIONS: TENS seems to be an effective and safe treatment for refractory OAB warranting randomized, placebo-controlled trials.

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ORIGINAL ARTICLE

Transcutaneous electrical nerve stimulation: an effective treatment for refractory non-neurogenic overactive bladder syndrome?

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Conclusions TENS seems to be an effective and safe treatment for refractory OAB warranting randomized, placebo-controlled trials.

Keywords Transcutaneous electrical nerve stimulation · Non-neurogenic overactive bladder syndrome

Introduction

Overactive bladder syndrome (OAB), also known as urgency syndrome or urgency-frequency syndrome, is characterized by urgency, with or without urgency incontinence, usually with frequency and nocturia, and there is no proven infection or obvious pathology [1]. OAB is highly prevalent and affects the lives of millions of people worldwide, i.e. approximately 15 % of women and 10 % of men, increasing with advancing age [2]. OAB has a major impact on quality of life and sexuality [2], and besides the debilitating manifestations for patients, OAB also imposes substantial economic burden on every healthcare system, as direct annual costs are comparable to those of other chronic diseases such as dementia and diabetes mellitus [3].

Although antimuscarinics are the pharmacological treatment of choice for OAB, the effectiveness is limited. In a recent systematic review and meta-analysis of randomized controlled trials [4], antimuscarinics led to a mean decrease in incontinence episodes of less than one episode per 24 h compared to placebo. In addition, many patients discontinue antimuscarinic treatment due to adverse events [5]. Thus, there is an urgent need for effective, well-tolerated

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therapeutic alternatives. Transcutaneous electrical nerve stimulation (TENS) is an established treatment for OAB in children [6, 7] and may also be a valuable option in adults. We therefore investigated, in a prospective study, the effect of TENS for treating adult patients with refractory OAB.

Patients and methods

Patients

A consecutive series of 42 patients who underwent TENS for refractory non-neurogenic OAB was prospectively evaluated. All patients had a complete urological evaluation before considering study enrolment including medical history, satisfaction assessment, physical examination, bladder diary for at least 48 h, urinalysis, urine culture, urethrocystoscopy, bladder washing cytology, and urodynamic investigation. Study inclusion criteria were non-neurogenic OAB with urodynamically proven detrusor overactivity, failed behavioural treatment and pharmacotherapy with at least 2 antimuscarinics, each for a minimum of 1 month and titrated to the maximum dose, no previous surgery for OAB, and no urodynamic signs of bladder outlet obstruction.

The study was performed in accordance with the ethical standards expressed in the Declaration of Helsinki. Before study inclusion, all patients were thoroughly informed, and informed consent was obtained. Urodynamic studies were performed according to Good Urodynamic Practices [8]. All methods, definitions and units conform to the standards recommended by the International Continence Society [1].

TENS treatment and follow-up assessment

Transcutaneous electrical nerve stimulation was performed at home with an Alpha 4 Conti (Danmeter A/S, 5000 Odense C, Danmark) stimulation device applying Periform® + vaginal electrodes (Mobilis Healthcare Group, Lancashire, UK) in women and PEN2 penile electrodes (Sugar International, Chevillon-sur-Huillard, France) in men (Fig. 1). Bipolar stimulation with 8 Hz and 400 μs at sensory threshold level was used for 20 min twice a day.

Effects of TENS treatment were evaluated by bladder diary for at least 48 h and by satisfaction assessment (i.e. very satisfied, satisfied/undecided/dissatisfied, very dissatisfied). In analogy to the sacral neuromodulation (SNM) literature [9, 10], success of TENS was defined as an improvement of more than 50 % in bladder diary variables (i.e. number of voids, voided volume, and number of leakages: at least 2 of these 3 variables had to have improved for considering a treatment success). After 12 weeks of treatment, TENS was discontinued in all patients and restarted (20 min twice a day) on patient's request in the case that OAB symptoms recurred.

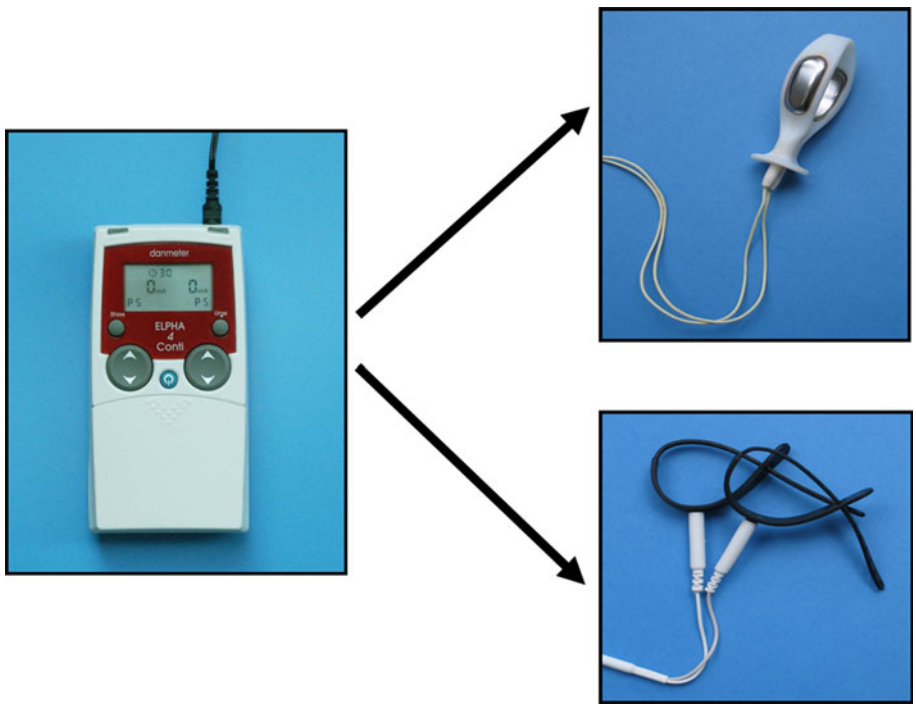

Fig. 1 Transcutaneous electrical nerve stimulation (TENS) device with vaginal and circular penile electrodes for treating refractory overactive bladder syndrome (OAB)

Outcome measures

Primary outcome measures were changes in the bladder diary and in the satisfaction assessment at baseline and after 12 weeks of treatment.

Secondary outcome measures were changes in the bladder diary and in the satisfaction assessment in patients with successful TENS at the last known follow-up.

Tertiary outcome measures were adverse events during TENS.

Statistical analysis

Data distribution was tested by Q–Q plots. Data were approximately normally distributed and are shown as the mean ± standard deviation (SD). For a calculated sample size of 41 patients, the study was designed to have 80 % power ($\beta = 0.2$) for the paired t-test to detect a difference of 2 voiding episodes and a difference of 50 mL in voided volume (these differences were estimated to be clinically relevant) before TENS versus during TENS at a 2-sided significance level of 2.5 % ($\alpha = 0.025$), assuming a standard deviation (SD) of about two times the detectable difference. The paired t-test and the McNemar's test were used to compare related samples, respectively. Comparing unrelated samples, the unpaired t-test was applied. Statistical analyses were performed using IBM® SPSS® Statistics version 19.

Table 1 Patient baseline characteristics

Characteristics	
Total number of patients	42 (100 %)
Women	25 (60 %)
Men	17 (40 %)
Mean age in years	48 (SD ± 16; range, 18–76)
Mean duration of OAB symptoms in years	3.2 (SD ± 1.6; range, 0.75–7.17)
Number of antimuscarinics used	
2	16 (38 %)
3	14 (33 %)
4	12 (29 %)
Reasons for quitting antimuscarinic therapy	
Insufficient effect	39 (93%)
Intolerable side effects	3 (7%)
Bladder diary variables	
Mean number of voids per 24 h	15 (SD ± 3.6; range, 9–26)
Mean voided volume	160 (SD ± 50; range, 90–300)
Number of incontinent patients	18 (43 %)
Number of pads used per 24 h (incontinent patients only)	3 (SD ± 1.4; range, 1–6)

SD standard deviation

Results

Baseline characteristics of the 42 patients (25 women, 17 men) treated with TENS for refractory non-neurogenic OAB are shown in Table 1.

Transcutaneous electrical nerve stimulation was successful following 12 weeks of treatment in 21 (50 %) of the 42 patients. The positive TENS effect was sustained during a mean follow-up of 21 months (SD ± 22; range, 6–83 months) in 18 (86 %) of the 21 patients. At the last known follow-up, 4 of the successfully treated patients were still under TENS; the 14 remaining had a sustained effect without treatment.

Following 12 weeks of TENS treatment, mean number of voids per 24 h decreased significantly ($p < 0.001$) from 15 (SD ± 3.6; range, 9–26) to 11 (SD ± 4.8; range, 5–26) and mean voided volume increased significantly ($p < 0.001$) from 160 mL (SD ± 50; range, 90–300) to 230 mL (SD ± 85; range, 90–370). In addition, 18 (43 %) of the 42 patients were incontinent before TENS. Following 12 weeks of TENS treatment, continence was completely restored in 7 (39 %) of the 18 incontinent patients, and the mean number of pads used per 24 h decreased significantly ($p = 0.001$) from 3 (SD ± 1.4; range, 1–6) to 1 (SD ± 1.7; range, 0–7).

Patients' satisfaction with the lower urinary tract function changed significantly, following TENS treatment ($p < 0.001$). Before TENS, all 42 patients were dissatisfied or very dissatisfied. Following 12 weeks of TENS treatment, 21 (50 %) patients felt satisfied or very satisfied.

In a subgroup analysis assessing potential gender impact, no significant differences ($p > 0.1$) between female and male patients were found.

No adverse events related to TENS occurred during the study period.

Discussion

Main findings

In patients with refractory non-neurogenic OAB, TENS was successful following a 12-week treatment period in 50 % of the patients, and of these, the positive effect was sustained in more than 80 %. Importantly, no adverse events related to TENS occurred during the study period. Thus, our findings indicate that TENS may be effective and safe for treating patients with refractory OAB. However, randomized controlled trials are lacking and are highly warranted.

Findings in the context of existing evidence

Neuromodulation, both non-invasive and invasive, has become a well-established and widely accepted treatment in recent years for patients with OAB. Although the exact mechanism of action remains to be elucidated, it seems to involve modulation of spinal cord reflexes and brain networks by peripheral afferents [11]. Dorsal clitoral nerve stimulation during bladder filling reduced the activation of certain cortical areas suggesting a neuromodulatory effect on supraspinal centres involved in lower urinary tract control [12]. In addition, plastic reorganization of cortical networks triggered by peripheral neuromodulation has been hypothesized [13]. In a PET study of patients treated by SNM for urgency incontinence [14], the authors proposed that acute neuromodulation predominantly involves areas associated with sensorimotor learning, which might become progressively less active during the course of chronic neuromodulation. Moreover, the sympathetic nervous system might play a role as indicated by studies of low-frequency pudendal nerve stimulation in cats with chronic spinal cord injury [15].

Percutaneous tibial nerve stimulation (PTNS) has been shown to be an effective treatment for non-neurogenic OAB in randomized, double-blind, placebo-controlled trials [16, 17]. In patients with refractory OAB, SNM was found to have clear benefits for carefully selected patients, but many adverse events were reported and redo surgery was often necessary [18–20]. Pudendal neuromodulation has emerged as an alternative to SNM, considering a randomized cross-over study reporting that stimulation of the pudendal nerve may be more effective than SNM for modulating bladder activity [21]. Since the pudendal nerves innervate many areas in the pelvic region including vagina, penis, anal and urethral sphincters, and the perineal skin, it is possible to stimulate these pudendal nerve branches non-invasively [22]. Previous animal studies have shown that vaginal [23] and penile stimulation [24] can inhibit bladder activity and prevent incontinence what is in line with the findings of the present study in humans. Thus, regarding the non-invasiveness, easy application, and excellent safety profile, TENS may become a valuable treatment option for refractory OAB before more invasive methods such as PTNS, intradetrusor botulinum-A-toxin injections or SNM are considered.

Implications for research

Considering the promising findings of the present study, further investigations are warranted. Randomized controlled trials are necessary to demonstrate the efficacy of TENS in treating OAB. In such prospective trials, both non-neurogenic and neurogenic OAB, validated disease- and condition-specific quality of life data, short-, medium- and long-term results as well as cost-effectiveness issues should be assessed, and outcomes should be reported with the Consolidated Standards of Reporting Trials statement [25]. Moreover, it would be interesting to directly compare TENS and PTNS. At a glance, PTNS seems to be more effective than TENS, considering the reported PTNS success rates of 55–71 % [16, 17]. However, taking into account the different inclusion criteria, the results are not comparable. The feasibility of TENS, which can be easily used at home by the patient, represents a real advantage compared to PTNS, which requires the insertion of a needle close to the tibial nerve. Furthermore, the genital nerves are in more proximity to the sacral plexus than the tibial nerve, and this may, at least from a theoretical viewpoint, have an effect on treatment efficacy. In addition, stimulation parameters need further investigation. Although the TENS device that applied in the present study allows a wide range of different stimulation settings, we preset the parameters and did them not adjust to each patient for homogeneity reasons. However, individual adjustment of the stimulation parameters in analogy to SNM may improve the response rate and warrants additional studies. There is also unclear whether a maintenance-therapy is needed or not. Indeed, treatment standardization is lacking, and there are no guidelines for therapeutic and maintenance regimens.

Implications for practice

Overactive bladder syndrome is a widespread chronic illness that has a major impact on quality of life, affecting emotional, social, sexual, occupational, and physical aspects of daily life [26]. Besides the debilitating manifestations for patients, it also imposes substantial economic burden for every healthcare system [3]. First-line treatment for OAB includes antimuscarinics, but the treatment effect is often unsatisfactory, so that other options have to be considered, including the yet unlicensed intradetrusor botulinum-A-toxin injections, SNM, or even more invasive procedures such as bladder augmentation or urinary diversion. Thus, easy, non-invasive, widely available, effective, and well-tolerated therapeutic alternatives are highly desirable. Considering the findings of the present study, TENS may become such a treatment option, especially taking into account that we only included patients with refractory OAB, i.e. all our patients had undergone multiple failed previous treatments (negative patient selection). In the case that our findings are confirmed in randomized trials, this would have major implications for daily practice since TENS would have to be propagated widely and implemented quickly as a standard OAB treatment.

Limitations

The present study has several limitations. First, the results are based on a non-randomized study without a control

group. Thus, we are not able to differentiate between the real TENS effect and the placebo effect. From a patient's viewpoint, however, it is most important that a treatment helps, independent of a potential placebo effect. Second, we did not assess patients' quality of life using a validated OAB-specific questionnaire. Third, including only patients with refractory non-neurogenic OAB may induce a negative selection bias. Indeed, the TENS effect may be underestimated in the present study and is probably more pronounced in patients with treatment-naive OAB. Moreover, it is unclear whether our results in non-neurological patients could be extrapolated to patients with neurogenic OAB, although promising results of transcutaneous posterior tibial nerve stimulation for treating OAB in multiple sclerosis patients have been found [27]. Fourth, the duration of the bladder diary may have influenced our results, i.e. a bladder diary of more than at least 2 days may result in more reliable data regarding patients' symptoms. However, it should be considered that patient compliance decreases with longer diary duration and that, despite recent attempts [28], there is no validated generally accepted bladder diary currently available [29].

Despite the addressed limitations, the present study was prospective with predefined outcome criteria, and it was adequately powered and sized to detect differences before versus during TENS treatment. In addition, the 42 evaluated patients with refractory non-neurogenic OAB with a mean follow-up of 21 months in the case of successful TENS treatment seem not insignificant, considering the lack of data published to date and taking into account the debilitating manifestations of OAB.

Conclusions

In patients with refractory non-neurogenic OAB, TENS was successful following a 12-week treatment period in 50 % of the patients, and of these, the positive effect was sustained in more than 80 % during a mean follow-up of 21 months. Importantly, no adverse events related to TENS occurred during the study period. Thus, TENS seems to be an effective and safe treatment for refractory OAB warranting randomized, placebo-controlled trials.

Conflict of interest None of the contributing authors has a conflict of interest in relation to this article.

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